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Using Simple Water:VACUUM Energetics to Model Phospholipid Bilayer Electropermeabilization
Jane HyoJin Lee, Zachary A. Levine, Mayya Tokman, P. Thomas Vernier, Michael E. Colvin.
Electropermeabilization (electroporation) occurs when a supraphysiological electric field is applied across the cell membrane, but this phenomenon is not yet accessible to direct experimental observation. Molecular dynamics simulations suggest that interfacial waters located at the water:lipid interface are key determinants of electric field-driven pore formation in phospholipid bilayers [1]. We compared poration dynamics in water:vacuum:water and water:lipid:water systems at varying external electric fields. Both systems form water columns bridging the vacuum or lipid-filled gaps that are similar in structure and energetic signature. We identify these columns as electropores and study their structure and dynamics at the emerging and mature stages in their evolution. The electropores in both systems appear to originate from structurally similar water intrusions. We report pore formation times for each system as a function of electric field, and dipole-dipole interaction energies between interfacial water molecules.
[1] Tieleman, D.P., The molecular basis of electroporation. BMC Biochemistry, 5:10, 2004.

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Molecular Dynamics Studies of Cu(II)-Bound -Synuclein(S) Complexes
Lurong Pan, James C. Patterson.
Parkinson's disease (PD) is one of the most common neurodegenerative diseases. The aggregation of α-Synuclein (αS) is thought to be one of the key pathological events in the pathology of PD. Elevated Cu(II) concentrations have been reported in the cerebrospinal fluid of PD patients and many in vitro studies show that Cu(II) bonds to αS on different sequences either promotes or prevents the aggregation process . However, there is disagreement over which residues preferentially bind Cu(II) and how Cu(II) affects the aggregation process. Residues Met1, Asp2, 119, 121, His50, Asn120, Glu123 have been suggested as the most stable Cu(II) binding sites. However, research has shown that αS aggregation begins in the NAC region (residues 61-95) where Cu(II) binding could also occur at residues Glu61 and Glu83. To gain more insight into the nature of Cu(II) binding and its role in αS aggregation, single-site binding models of Cu (II) to all the aforementioned suggested residues were created using the NMR solution structure of αS and quantum mechanics calculations on the Cu(II) coordination environment. Also, Cu(II)-bound dimeric structures of just the NAC region were built and compared with those of the Cu(II)-free NAC dimer. Molecular dynamics simulations were performed and the energetics as well as dynamic structures were monitored.

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A Heterogeneous, Purpose Built Computer Architecture for Accelerating Biomolecular Simulation
Christopher A. Madill, Arun Patel, Manuel Saldaña, Paul Chow, Régis Pomès.
Molecular dynamics (MD) is a powerful computer simulation technique providing atomistic resolution across a broad range of time scales. In the past four decades, researchers have harnessed the exponential growth in computer power and applied it to the simulation of diverse molecular systems. While simulations are currently approaching the hundred-thousand-atom, millisecond-timescale mark using large-scale computing centres, many interesting research topics are still beyond the reach of practical computational biophysics efforts. The purpose of this work is to design a high-speed MD machine which outperforms standard simulators running on commodity hardware or on large computing clusters. In pursuance of this goal, an MD-specific computer architecture is developed which tightly couples the fast processing power of Field-Programmable Gate Array (FPGA) computer chips with a network of high-performance CPUs. The development of this architecture is a multi-phase approach. Core MD algorithms are first analyzed and deconstructed to identify the computational bottlenecks governing the simulation rate. High-speed, parallel algorithms are subsequently developed to perform the most time-critical components in MD simulations on specialized hardware much faster than is possible with general-purpose processors. Finally, the functionality of the hardware accelerators is expanded into a fully-featured MD simulator through the integration of novel parallel algorithms running on a network of CPUs. With initial acceleration efforts focused primarily on expensive nonbonded force calculations, an architecture was developed whereby a single machine achieves the performance equivalent of an 88-core InfiniBand-connected network of CPUs. Finally, a methodology to successively identify and accelerate the remaining time-critical aspects of MD simulations is developed. This leads to an architecture with a projected performance equivalent of nearly 150 CPU-cores, enabling supercomputing performance in a single computer chassis, plugged into a standard wall socket.

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Using Molecular Dynamics to Measure Transmembrane Protein Diffusion
Allison Dickey, Mark Stevens.
A number of recent experimental and theoretical studies have examined the relationship between protein diffusion rate in lipid membranes and the protein radius (R). Ramadurai et al. measured the diffusion coefficients for transmembrane proteins using fluorescence correlation spectroscopy and they found that protein diffusion has a ln(1/R) dependence.[1] This indicates that protein diffusion is weakly dependent on R, which agrees with the Saffman-Delbrück model.[2] Previously, Gambin et al. measured transmembrane peptide and protein diffusion coefficients using fringe pattern photobleaching and found that the diffusion has a 1/R dependence.[3] To understand this deviation from the Saffman-Delbrück model, Naji et al. conducted a theoretical study and concluded that if protein-lipid interactions cause a local membrane deformation, then the protein mobility will decrease since the protein movement is correlated with the movement of the deformed patch of membrane. This results in a diffusivity dependence of 1/R.[4] We have used coarse-grained molecular dynamics simulations to further examine protein diffusion in a fluid lipid bilayer. To obtain accurate statistics at dilute protein concentrations, we have used two methods to calculate protein diffusion. For bilayers that contained a single protein, we calculated the protein mobility by applying a force to the protein. From the mobility and the Stokes-Einstein equation, we obtained the protein diffusion coefficient. For dilute bilayers that contained more than one protein, we calculated the diffusion coefficient from the 2D Einstein equation. We have also measured lipid behavior as a function of distance from the protein surface. We will compare our simulation data with experiment and analytic theory.
1. J. Am. Chem. Soc. **2009**, *131*, 12650.
2. Proc. Natl. Acad. Sci. USA. **1975**, *72*, 3111.
3. Proc. Natl. Acad. Sci. USA. **2006**, *103*, 2098.
4. Biophys. J. **2007**, *93*, L49.

811-Pos Board B611
Griffin: A Versatile Methodology for Optimization of Protein-Lipid Interfaces for Membrane-Protein Simulations
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As new atomic structures of membrane proteins are resolved, they reveal increasingly complex transmembrane topologies, and often highly irregular surfaces with crevices and pores. In many cases, specific interactions with the lipid membrane are formed and are functionally crucial, as is the overall lipid composition. Compounded with increasing protein size, these characteristics pose a challenge for the construction of simulation models of membrane proteins in lipid bilayers; clearly, that these models are sufficiently realistic bears upon the reliability of simulation-based studies of these systems. Here, we introduce GRIFFIN, a versatile, grid-based force-field input for molecular dynamics simulations, which we employ to automate and optimize a membrane-embedding protocol. Initially, this protocol carves out lipid and water molecules from a volume equivalent to that of the protein, so as to conserve the system density. In the subsequent optimization phase GRIFFIN adds an implicit protein force field to a molecular-dynamics simulation of the pre-carved membrane. In this force field, any lipid or water atoms inside the implicit protein volume experience an outward force that will expel them from that volume, whereas molecules outside are subject to electrostatic and van-der-Waals interactions with the implicit protein. At each step of the simulation, these forces are updated by GRIFFIN and combined with the intermolecular forces of the explicit lipid-water system, to derive a trajectory of the atomic positions. This procedure enables the construction of realistic and reproducible starting configurations of the protein-membrane interface within a reasonable timeframe and with minimal intervention. GRIFFIN is a standalone tool and is designed to work alongside any existing molecular dynamics package, such as NAMD or GROMACS.

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Simulation Studies of Wimley-White Peptides
Gurpreet Singh, D. Peter Tieleman.
Hydrophobicity scales for amino acids are routinely used for the prediction of transmembrane regions in membrane proteins. Wimley et al. developed one such hydrophobicity scale for amino acids, by measuring the partitioning of WLXLL pentapeptides at the POPC-Water interface, where X was replaced by each of the 20 amino acids.
In this study, we use Molecular Dynamics (MD) simulations to further characterize these peptides with atomistic details. MD simulations of Wimley-White peptides were carried out at POPC-water and cyclohexane-water interfaces. The distributions of amino-acid side-chains were calculated and compared with coarse-grained MARTINI simulations. Free energy perturbation methods were used to measure the hydrophobicity scale using the MARTINI force field and the results are compared with experimental data.